

### REMARKS

This document is filed in response to the non-final Office Action dated June 25, 2009 (“Office Action”).

At the Examiner’s suggestion, Applicant has amended the Specification to capitalize trademarks recited therein and to correct obvious errors. In particular, Applicant has amended the paragraph beginning at page 30, line 2 to replace the term “graft versus disease” with “graft versus host disease.” The paragraph lists a number of TNF and IL-1 dependent disorders, some of which involve inflammation or the immune system. It is well known that “graft versus host disease” is a disorder involving inflammation or the immune system.<sup>1</sup> On the other hand, “graft versus disease” refers to a beneficial effect, but not a disorder.<sup>2</sup> In view of this knowledge and the minor typographical difference between “graft versus disease” and “graft versus host disease,” one skilled in the art would realize that “graft versus disease” is an error and should read “graft versus host disease.” In this connection, Applicant would like to point out:

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

See MPEP 2163 IB.<sup>3</sup>

Applicant has amended claim 1 to incorporate the limitation of original claim 12, and has amended claims 3, 6, and 10 to remove the term “functional equivalents.” Claim 6 has been amended to more particularly point out the claimed invention, support for which is found in the Specification at page 2, line 14. Claim 19 has been amended to promote clarity. Claim 20 has been amended to change its dependency. Applicant has added new claims 27 and 28, support for which can be found in the Specification at page 30, lines 6-10. Claims 11 and 12 have been cancelled.

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<sup>1</sup> This disease is a complication arising from tissue transplantation, where immunological cells in the grafted tissue mount an attack against the host. See the Medline Plus article on graft versus host disease; attached as Exhibit A.

<sup>2</sup> See e.g., <http://www.cancerhelp.org.uk/help/default.asp?page=25868>. A printout copy of this website is attached as Exhibit B

<sup>3</sup> In *In re Oda*, the United States Court of Customs and Patent Appeal, in reversing a Board’s 35 U.S.C. § 112, first paragraph rejection, held that “changing of ‘nitrous’ to ‘nitric’ did not involve ‘new matter’ as “one skilled in the art would appreciate not only existence of error in specification of invention but also how to correct [the] error.”

No new matter is introduced. Upon entry of the proposed amendments, claims 1-10 and 13-28 will be pending. Among them, claims 22-24 have been withdrawn from further consideration for covering a non-elected invention and claims 1-10, 13-21, and 25-28 will be under examination. Applicant respectfully requests that the Examiner reconsider this application in view of the following remarks.

#### Claim Objection

The Examiner objects to claim 19 for informalities. See the Office Action, page 3, line 7. Applicant has amended claim 19 in the manner suggested by the Examiner and requests withdrawal of this objection.

#### Rejections under 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner rejects (1) claims 6, 7, and 10-12, and (2) claims 19-21 for lack of enablement. Applicant will address each of these two rejections below.

#### I

The Examiner rejects claims 6, 7, and 10-12, stating that while the Specification is “enabling for chimeric proteins comprising the domains recited in claim 1, [it] does not reasonably provide enablement for ‘functional equivalents’ of these domains.” See the Office Action, page 3, lines 13-15.

In the sole interest of moving this case forward, Applicant has amended claims 6 and 10 to remove the term “functional equivalents,” and cancelled claims 11 and 12. In view of these amendments, Applicant submits that this ground for rejection is moot and requests removal of the rejection.

#### II

The Examiner rejects claims 19-21, stating that the Specification is non-enabling for methods of treating a TNF- and IL-1-dependent disorder. See the Office Action, page 4, lines 6-8. Applicant respectfully traverses and will discuss claim 19 first.

Claim 19 covers a method of treating a TNF- and IL-1-dependent disorder by administering to a subject a pharmaceutical composition that contains a chimeric polypeptide of claim 1. The chimeric polypeptide of amended claim 1 includes, among others, SEQ ID NO: 2,

i.e., TNFRII-Fc-IL-1ra. The Examiner asserted that claim 19 is not enabled for four reasons, which will be addressed below.

A

The Examiner asserts that “the breadth of [claim 19] is excessive.” To support this assertion, he states that this claim is drawn to the treatment of “any TNF- and IL-1 related disorder.” See the Office Action, page 4, lines 16-19; *emphasis added*.

Applicant disagrees and would like to point out that the “disorder” recited in claim 19 does not cover all disorders that are “related” to TNF and IL-1 as construed by the Examiner. Instead, claim 19 is drawn to a method of treating a “TNF- and IL-1-dependent disorder.” As disclosed in the Specification, these disorders are all “associated with an abnormal level of the gene expression or activity of TNF or IL-1.” See page 30, lines 4-6. Examples of these disorders include acute and chronic inflammation (e.g., osteoarthritis, psoriatic arthritis, and rheumatoid arthritis), psoriasis, acute hepatitis, cardiovascular disease, graft versus host disease, and brain injury resulting from trauma, epilepsy, hemorrhage, or stroke. See page 30, lines 6-10. As these disorders are all associated with abnormally high levels of TNF or IL-1 expression or activity, they all can be treated by neutralizing TNF activity and antagonizing IL-1 receptor activity. Clearly, contrary to the Examiner’s assertion, claim 19 covers a method of treating a small genus of disorders. Thus, Applicant submits that the breadth of claim 19 is not excessive.

B

It is the Examiner’s position that the Specification is not enabling for claim 19 as it “does not provide any guidance or working examples that the claimed chimeric protein ... is able to treat any disease.” See the Office Action, page 4, lines 16-19. This position is, in part, based on his belief that the Specification “only demonstrate[s] *in vitro* work.” See the Office Action, page 4, line 28. Applicant respectfully traverses.

First, Applicant notes that the Specification discloses *in vivo* results demonstrating that the claimed method is effective in treating diseases associated with abnormal levels of TNF or IL-1 activity. The Specification teaches that systemic administration of a composition that contains the chimeric polypeptide TNFRII-Fc-IL-1ra effectively treated skin inflammation in mice. See page 39, lines 10-18. Further, as disclosed in this passage, this treatment was

significantly more effective than a method using a commercially available chimeric polypeptide. Additionally, the Specification teaches that systemic administration of a composition that comprises TNFR1I-Fc-IL-1ra effectively treated clinical arthritis in mice. Again, the treatment was significantly more effective than a method using a commercially available chimeric polypeptide. See page 39, line 19 to page 40, line 5. In view of these teachings, Applicant submits that the Examiner's position is groundless.

Second, as discussed immediately above, the Specification discloses working examples for treating arthritis and skin inflammation, two representative examples of TNF- and IL-1-dependent disorders. Applicant reminds the Examiner, "representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." See MPEP 2164.02. For the following reasons, Applicant submits that the Specification is also enabling for treating other members in the genus of TNF- and IL-1-dependent disorders.

Further, as the above-mentioned arthritis and skin inflammation are examples of TNF- and IL-1-dependent disorders, they are associated with abnormally high levels of TNF or IL-1 expression or activity. Administering a pharmaceutical composition that contains a chimeric polypeptide of amended claim 1, effectively treated the two disorders by neutralizing TNF activity and antagonizing IL-1 receptor activity. Accordingly, a skilled artisan would understand that neutralizing TNF activity and antagonizing IL-1 receptor activity would likewise treat other members in the genus of TNF- and IL-1-dependent disorders via the same mechanism. In other words, without undue experimentation, he or she would be able to effectively treat other members of the genus using a pharmaceutical composition that contains a chimeric polypeptide of amended claim 1. For the foregoing reasons, Applicant submits that claim 19 is enabled in its full scope even though the Specification only provides experimental evidence for two representative examples of the genus of TNF- and IL-1-dependent disorders.

C

The Examiner also rejected claim 19, stating that Figures 8 and 9 and Table 3 in the Specification do not support the efficacy of the above-discussed chemic polypeptide. See the Office Action, page 4, lines 19-23. The figures and table at issue present IL-1 and TNF neutralization data, comparing a specific chemic polypeptide, TNFRII-Fc-IL-1ra, with IL-1ra and TNFRII-Fc, which are effective in neutralizing IL-1 and TNF. It appears to be the Examiner's position that claim 19 is not enabled because the figures show that TNFRII-Fc-IL-1ra "is less potent" than L-1ra and TNFRII-Fc. Applicant disagrees for at least two reasons.

First, contrary to the Examiner's position, the figures do not indicate that that TNFRII-Fc-IL-1ra "is less potent" than L-1ra or TNFRII-Fc neutralizing IL-1 or TNF. Specifically, the concentrations in the figures are "µg/ml" or "ng/ml." As such, the figures compare the efficacies of TNFRII-Fc-IL-1ra, L-1ra, and TNFRII-Fc in term of weights of the three proteins, but not numbers or mole numbers of them. Given the fact that the molecular weight of TNFRII-Fc-IL-1ra, a fusion protein, is much higher than those of both L-1ra and TNFRII-Fc, one skilled in the art could appreciate that TNFRII-Fc-IL-1ra is not less potent, but more potent, than L-1ra or TNFRII-Fc in term of mole numbers.

Second, even if TNFRII-Fc-IL-1ra "is less potent" than L-1ra or TNFRII-Fc, which Applicant does not concede, this does not render claim 19 unenabled. In fact, as mentioned above and in the Specification, both L-1ra and TNFRII-Fc are themselves effective in neutralizing IL-1 and TNF, respectively. Being "less potent" of a protein than them does not mean such a protein is not effective. To the contrary, the data presented in the figures and the table mentioned above show that the efficacy of TNFRII-Fc-IL-1ra is at least comparable to or more potent than those of L-1ra and TNFRII-Fc. In view of these data, one skilled in the art would appreciate that TNFRII-Fc-IL-1ra is effective and potent for the method of claim 19.

For the above reasons, Applicant submits that the Examiner's position is untenable.

D

The Examiner states, "in the examples, Applicant[] use[s] the full-length TNFR and IL-1[r]a proteins. However, the claims are drawn towards using only the neutralizer and receptor antagonist domains ...[yet] only the full length proteins were shown to be effective." See the Office Action page 4, lines 24-28; *emphasis added*. Thus, the Examiner considers claim 19 as

non-enabled where “less than the full-length proteins” are used. See the Office Action, page 5, lines 1-2. Applicant submits that the Examiner’s ground rejection is moot in view of amendments made to the claims. Specifically, claim 19 covers a method of treating a TNF- and IL-1-dependent disorder by administering a pharmaceutical composition that contains a chimeric polypeptide of amended claim 1. The chimeric polypeptide of amended claim 1 includes the sequence of SEQ ID NO: 2, which was “shown to be effective” in the above-described working examples.

In view of the above remarks, Applicant submits that the Specification is enabling for claim 19 in its full scope. Claims 20 and 21 and new claims 27 and 28, dependent from claim 19, simply recite specific TNF- and IL-1-dependent disorders. For at least the reasons set forth above, they all meet the enablement requirement.

#### Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 6, 7, and 11 for indefiniteness and suggests that Applicant indicates that “IL-1ra” is the abbreviation for “IL-1 receptor antagonist” in claim 1, part (2). See the Office Action, page 5, lines 9-12.

Applicant points out that claim 1, part (2) recites “an IL-1 receptor antagonist domain.” This domain represents a part of the claimed polypeptide which acts as an antagonist of an IL-1 receptor. “IL-1ra” is a particular polypeptide having that activity. Accordingly, it would be improper to amend claim 1 as suggested by the Examiner. Instead, Applicant has amended claim 6, which is the first claim reciting an IL-1ra polypeptide, in the manner suggested. In view of the amendment, Applicant submits that this rejection has been overcome.

#### Rejections under 35 U.S.C. § 103

The Examiner rejects claims 1-11, 13-21, 25, and 26 for obviousness. See the Office Action, page 5, item 3. Applicant notes that claim 12 is not rejected for the same reason. In other words, claim 12 is non-obvious. In the sole interest of moving this case forward, Applicant has amended claim 1 to incorporate the limitation in original claim 12 and cancelled claims 11 and 12. In view of this amendment, Applicant submits that claim 1, as amended, is non-obvious. Claims 2-10, 13-21, 25 and 26 depend from amended claim 1. For at least the same reason, they are also non-obvious. Applicant requests withdrawal of the rejection.

### Rejections Under 35 U.S.C. § 101

The Examiner provisionally rejects claims 1-21, 25, and 26 for non-statutory obvious-type double patenting over (1) claims 1-5, 10, 13-15, 17, and 19-22 of co-pending US Patent Application No. 11/576,963, which claims priority to US Provisional Patent Application No.: 60/618,476, filed October 12, 2004; and (2) claims 1, 12-16, 18, and 20-24 of co-pending US Patent Application No.: 11/996,816, which claims priority to US Provisional Patent Application No.: 60/703,950, filed July 29, 2005. See the Office Action, page 8, lines 1-3 and lines 9-11.

Applicant notes that present application claims priority to PCT/US04/27655 filed August 25, 2004. Clearly, the present application is the earliest filed application of the three co-pending applications.

Assuming that the other rejections discussed above have been overcome, Applicant submits that these two provisional double patenting rejections are the only remaining rejections. In this regard, Applicant turns to MPEP § 804 IB1, which states, “[i]f a ‘provisional’ nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed [application,] the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.” As the present application is the earliest-filed application and all other rejections have been overcome, the Examiner should withdraw the above-mentioned provisional ODP rejections and issue this application as a patent.

### CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

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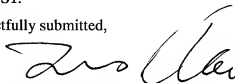
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No fees are believed to be due. Please apply any other charges to Deposit Account No. 50-4189, referencing Attorney Docket No. 50046-003US1.

Date: \_\_\_\_\_

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Respectfully submitted,



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